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Neuromodulation of right auditory cortex selectively increases activation in speech-related brain areas in brainstem auditory agnosia

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ABSTRACT

Background: Auditory agnosia is an inability to make sense of sound that cannot be explained by deficits in low-level hearing. Based on recent promising results in the area of neurorehabilitation of language disorders after stroke, using transcranial direct current stimulation (tDCS), we examined a young patient with general auditory agnosia due to traumatic injury to the left inferior colliculus.

Methods: In this unique case we studied activations to sound embedded in a block design using fMRI before and after application of anodal tDCS to right auditory cortex.

Results: Before tDCS auditory discrimination deficits were associated with abnormally reduced activations of auditory cortex and bilateral unresponsiveness of the anterior superior temporal sulci and gyri. This session replicated a previous functional scan with the same paradigm a year before the current experiment. We then applied anodal tDCS over right auditory cortex for 20 minutes and immediately re-scanned the patient. We found increased activation of bilateral auditory cortices, and for speech sounds, selectively increased activation in Broca's and Wernicke's areas.

Conclusions: Future research may carefully consider the long-term behavioral effects after neurostimulation in auditory agnosia and its potential use in the neurorehabilitation of more general auditory disorders.

Key words: auditory agnosia, inferior colliculus, sound recognition, tDCS

AC-PC = anterior commissure – posterior commissure

BOLD = blood oxygenation level dependent

CT scan = computerized tomography scan

dB SPL(C) = decibel of sound pressure level (C-weighting)

fMRI = functional magnetic resonance imaging

FOV = field of view

FWE = family-wise error

hA1 = human primary auditory cortex

hR = rostral subarea of human primary auditory cortex

NHS = National Health Service (of the United Kingdom)

tDCS = transcranial direct current stimulation

TE = echo time

TR = repetition time

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a form of neurostimulation that uses mild constant electrical currents to the brain area of interest via electrodes on the scalp. It is a relatively new brain stimulation technique and is used to explore causal relationships between brain regions and cognitive functions predominantly in healthy participants. tDCS-induced neuromodulatory changes have been observed in a variety of domains, for instance, motor control (Sehm, Kipping, Schafer, Villringer, & Ragert, 2013), visual working memory (Heimrath, Sandmann, Becke, Müller, & Zaehle, 2012) and language (Iyer et al., 2005). The mechanisms of tDCS are still debated but it is currently thought that applying anodal tDCS to a particular brain region leads to increased cortical excitability in that region while applying cathodal tDCS leads to a decrease (Nitsche & Paulus, 2000, 2001). Polarity and various additional variables affect brain excitability including stimulation intensity and duration, cortical neurochemicals and even genetics (Price, McAdams, Grossman, & Hamilton, 2015).

tDCS has been used for therapeutic purposes in various clinical populations due to its ability to induce prolonged brain excitability. The rationale is that if a clinical condition occurs due to altered activity within a particular brain region then normalizing this activity with tDCS should lead to improvements in that condition (Sale, Mattingley, Zalesky, & Cocchi, 2015). More specifically, in the field of aphasia rehabilitation post-stroke, the rationale of applying tDCS to recover language is most frequently based on a model of interhemispheric rivalry between the residual speech areas in the damaged left hemisphere and intact right hemisphere (Holland & Crinion, 2012; Otal, Olma, Floel, & Wellwood, 2015). According to this model impaired speech is due to reduced output from the damaged, left hemisphere and/or inhibition of the left hemisphere from the intact, right hemisphere. Improvements in aphasic patients may therefore be obtained by increasing the excitability in the damaged, left hemisphere or dampening the output of the intact hemisphere. In accordance with this model Monti et al. (2008), for example, applied tDCS over the damaged left frontotemporal site in chronic aphasia patients. Performance on a picture naming task was assessed before and after tDCS with cathodal stimulation enhancing accuracy on the task by over 30%. The authors concluded that the improvement could be due to disinhibition of the damaged cortex, in line with the model of interhemispheric rivalry.

In contrast, others have obtained performance improvements with anodal tDCS to the contralesional hemisphere. The rationale here is boosting a mechanism in the right hemisphere for language recovery after stroke. For example, long-term treatment success for anomia is best predicted by activity increases in the right-sided Wernicke's homologue (Menke et al., 2009). In addition, the right hemisphere seems to play an important role in the recovery from post-stroke aphasia whereby right temporal activation has been linked to auditory sentence comprehension (Crinion & Price, 2005). For this reason, Floel et al. (2011) applied

anodal, cathodal and sham tDCS over right temporoparietal cortex in chronic aphasia patients but only anodal stimulation resulted in a significant and consistent improvement during language training. tDCS studies in the field of language rehabilitation are heterogeneous with respect to stimulation site, polarity, duration and task (Monti et al., 2013).

More recently, tDCS has been used in the rehabilitation of a patient with more general auditory problems after suffering from brainstem encephalitis during childhood (Mori et al., 2016). This patient suffered from bilateral hearing impairment, which was worse in her right ear. Anodal tDCS was applied to left auditory cortex, which improved her speech discrimination performance after only one application. This finding suggests that other neurological problems resulting in more general auditory perception disabilities may benefit from anodal tDCS and support neurorehabilitation efforts.

Here we report the effects of anodal tDCS over right auditory cortex on brain activity in a patient with auditory brainstem agnosia (Poliva et al., 2015). This young patient suffered damage to her left inferior colliculus and its brachium. The lesion led to partial de-afferentation of her auditory cortex, particularly on the left side, resulting in partial interruption of her auditory pathways and thereby causing a general auditory agnosia. A functional scan of her brain response to different sound categories (e.g. speech, environmental sounds) revealed activations of bilateral caudal subareas of her primary auditory cortex (hA1) and right posterior superior temporal gyrus but the rostral subarea of her primary auditory cortex (hR) and anterior superior temporal sulci and gyri were unresponsive compared to control participants. Thus while her auditory ventral stream seems dysfunctional her residual auditory ability is supported by a largely preserved auditory dorsal stream. Given the promising rehabilitation results for language and more general auditory disorders as well as the enhancement in performance of more basic auditory abilities with tDCS (Ladeira et al., 2011) the aim was to explore if tDCS has beneficial effects in recovering some activity in bilateral auditory cortices and association areas after anodal tDCS. We decided, in the first instance, to recommend a trial of anodal stimulation to the less affected, contralesional hemisphere. The rationale was based on the findings that long-term training success for naming objects was best predicted by increased activation in right-sided Wernicke's homologue (Menke et al., 2009) in post-stroke aphasic patients as well as trying to increase reactivity to sound in the less affected, contralesional auditory cortex.

METHODS

Case ML

At the age of 17, ML sustained a closed head injury. A CT scan revealed a hemorrhage in the right basal ganglia and dorsal midbrain. Her chief disability is a severe, auditory agnosia for

speech and environmental sounds due to avulsion of the left inferior colliculus. She has some motor impairment due to diffuse axonal injury but is functionally independent. Her medical history, neurological examination, neuroimaging and detailed auditory assessment has been reported (Poliva et al., 2015). MR-imaging reveals a cystic cavity in the right putamen at the site of the previous hemorrhage. There is a small periventricular lesion on the right lower pons, in the region of the inferior cerebellar peduncle. There is nearly complete avulsion of the left inferior colliculus, sparing only its most medial and caudal parts, and destruction of the brachia of the superior and inferior colliculi with the lesion extending into the red nucleus encroaching on the medial border of the left medial geniculate nucleus. The lesion has led to partial deafferentation of the auditory cortex, particularly on the left side. ML has been under the neurological care of the senior author, RDR, since the injury.

While her responses during pure tone audiometry were inconsistent, otoscopy, tympanometry and otoacoustic emissions were normal in both ears suggesting normal middle and inner ear function. Auditory brainstem response testing performed at 85dB eight months post-injury revealed normal wave I and III latencies in both ears. However, Wave V was absent after right ear stimulation and delayed after left ear stimulation in line with the imaging evidence of a lesion in the inferior colliculus. Probabilistic tractography confirmed that ML had preserved bilateral thalamic connectivity to the auditory cortex by showing that her functional anisotropy values were similar to those of a healthy control group (see Poliva et al., 2015 for details).

According to behavioral tests ML suffered from auditory extinction as assessed with a dichotic listening task, an impaired ability to localize sound, and poor auditory temporal resolution (Poliva et al., 2015). However, while ML's recognition of sound was poor, her performance of identifying spoken words and environmental sounds improved significantly (from 13% to 73% correct) with a four-alternative forced-choice design suggesting a partially preserved ability to perceive sounds. The research protocol was approved by ethics committees of Bangor University and the NHS and was in compliance with the Helsinki Declaration. We obtained written informed consent to participate and to publish the fully anonymized data from patient ML (for details see supplementary section).

fMRI paradigm, acquisition and analysis

We scanned ML (age = 28 years) before and after tDCS on a block design based on the "voice localizer" (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000) which we modified to include blocks of speech sounds. It consisted of four sound categories, each presented as twenty 10-second blocks, i.e. vocal non-speech sounds (e.g. laughs, coughs), verbal sounds (different words), environmental sounds (e.g. car engine, doorbell) and silent baseline. Sounds were presented via headphones (NordicNeuroLab) at 85dB SPL(C) and superimposed on scanner noise.

Each block started with 2s of silence followed by 8s of different stimuli of the same category. The eighty blocks were presented pseudo-randomly (i.e. no presentation of two same-category blocks in succession). We obtained a structural scan in each MRI session. The first MRI scans, tDCS and the second MRI scans were carried out within approximately one hour.

Scans were performed on a 3T-Philips Achieva with 8-channel head coil. The T2*-weighted scan consisted of an echo-planar imaging sequence in interleaved ascending order (32 axial slices, voxel size: 3mm³; flip angle: 90°; FOV = 240; TR = 2s; TE = 30ms; 400 volumes plus 20 volumes of additional rest at the end; 14 minutes). We then performed a whole-brain T1-weighted scan (voxel size: 1mm³; flip angle: 8°; FOV = 240; TR = 12ms; TE = 3.5ms; 5 minutes).

Data were analyzed in native space using SPM8 (Friston, Ashburner, Kiebel, Nichols, & Penny, 2006). Pre-processing consisted of AC-PC alignment, corrections for head motion (spatial realignment; trilinear interpolation), co-registration and spatial smoothing by applying a Gaussian kernel of 6mm full width at half maximum. Our SPM matrix contained three regressors of interest (voice, speech and environmental sounds) and movement parameters as regressors of no interest for each tDCS session. We calculated t-contrasts for pre- vs post-tDCS sessions (i.e. areas which responded more or less after tDCS across all sound categories and specifically in each category). Results are from a whole-brain analysis and reported at an extent threshold of $k > 35$ voxels and FWE-corrected at the cluster level with a threshold of $p < .05$.

tDCS delivery

Following the first MRI session we delivered tDCS using a Magstim DC-Plus stimulator, using saline-soaked sponge-covered rubber electrodes. Electrode positions were determined using the 10-20 international electrode placement system. The anode (5 x 5cm) was placed at position T4, which overlies the right temporal lobe (Koessler et al., 2009), and the cathode (5 x 7cm) was placed horizontally over the contralateral orbit. The Comets toolbox (Jung, Kim, & Im, 2013) was used to model the electric field resulting from this montage over a 'standard' brain and showed the concentration of energy in the intended location of auditory cortex. A current of 1.5mA was delivered for 20 minutes during which ML performed no experimental task but her cutaneous sensations were monitored.

RESULTS

Auditory temporal resolution was measured immediately before and after tDCS using a brief two-click fusion test and was unchanged (see supplementary results for more details including delayed effects of tDCS on ML's subjective hearing ability on the following day). Pre-tDCS, primary auditory cortex field hA1 was active but hR, anterior superior temporal gyri and sulci

were unresponsive to sound at a threshold of $p < .001$ (uncorrected; $k = 0$) replicating a previous scan one year earlier with the same paradigm (Poliva et al., 2015). Contrasting the two most recent fMRI sessions, we found greater BOLD activation in bilateral auditory cortices to all sounds against a silent baseline after anodal tDCS was applied (green; left: $k = 224$, $T = 9.95$, $p < .001$; right: $k = 348$, $T = 7.22$, $p < .001$) compared to before tDCS (blue; left: $k = 82$, $T = 4.95$, $p < .001$; right: $k = 156$, $T = 8.48$, $p < .001$; Figure 1A). We also saw a selective increase in activation to speech post-tDCS (speech pre-tDCS < speech post-tDCS; Figure 1B) in left inferior frontal gyrus ($k = 66$, $T = 4.44$, $p < .001$; Broca's area) and posterior superior temporal sulcus ($k = 86$, $T = 4.95$, $p < .001$; Wernicke's area). We found no specific effects of tDCS to environmental and vocal sound categories and no increased activations for any of the reverse contrasts (i.e. post-tDCS < pre-tDCS).

FIGURE 1 ABOUT HERE

DISCUSSION

We examined whether a patient with brainstem auditory agnosia might benefit from anodal tDCS to the less affected hemisphere given encouraging reports in the language rehabilitation literature. We scanned our patient before and after anodal tDCS over right auditory cortex while passively listening to different sound categories including speech. Before the application of tDCS much of auditory cortex was unresponsive bilaterally independent of sound category which is in line with ML's inability to reliably recognize and discriminate sound objects. After the application of tDCS, BOLD activation increased along primary auditory cortices medially and along the superior temporal gyri and sulci. We also found selective activation to speech sounds in Broca's and Wernicke's area when there was no selective activation to any of the sound categories before the application of tDCS. Our results highlight the potential of tDCS to selectively increase blood flow but it remains to be seen what this increased brain response means in terms of function.

It is important to note that an increase in MRI activation after tDCS is unlikely to be due to a repetition in testing. This is because the test re-test reliability of activation in the superior temporal sulcus for the voice localizer is high (intra-class correlation > 0.9) (Pernet et al., 2015). It is also noteworthy, that the pattern of activation is not due to differences in head motion between the two MRI sessions as patient ML was instructed to stay as still as possible and movement parameters were included in the models. Head motion was also within 2.5mm along x, y and z-axes in both sessions (i.e. comparable to scanning sessions of young, healthy individuals).

Patient ML's performance on a very brief 2-click fusion test remained unchanged after the administration of tDCS. While there were practical reasons why we did not examine the patient on a more sensitive and extensive test battery during this pilot administration of tDCS, it makes it difficult to speculate what the increased activation in auditory cortex, and in particular enhanced differential activation to speech, may reflect. Jäncke et al. (1998) has shown that increased sound intensity (i.e. sound pressure level) results in increased fMRI response in bilateral primary and secondary auditory cortices and bilateral inferior frontal gyri to verbal and non-verbal stimuli. tDCS to right auditory cortex may have affected sound intensity perception by triggering increased efferent corticofugal activity and thereby affected auditory cortical processing. This explanation however, cannot explain the *differential* activation to sounds of the speech category compared to other sound types. Future studies, initially with healthy participants, will need to carefully investigate what this increased fMRI response after tDCS to speech may reflect, ideally using a psychophysics approach (e.g. Bestelmeyer et al., 2011).

We originally collected this data as a pilot for a therapeutic trial of tDCS over the course of a week. Prior to starting such a trial we wanted to ensure that ML tolerates tDCS well. On the day of testing ML reported no adverse effects of tDCS. However, on a follow-up visit a week later she mentioned that her ability to understand speech seemed worse for a couple of days after the day of her visit. This subjective report of delayed worsening of auditory perception is difficult to interpret and may be due to a number of different factors not necessarily related to our testing. We are not aware of similar reports in the literature describing a delayed worsening in performance. However, given this report we decided not to proceed with any further brain stimulation of this patient and exploration of tDCS-induced behavioral effects.

Our findings are in line with models describing dual pathways in the auditory system known as the dorsal and ventral processing streams for the analysis of spatial location and object (including speech) processing, respectively (Bizley & Cohen, 2013). ML's auditory agnosia seems to be caused by damage to the auditory ventral stream. tDCS led to partial "normalization" of brain activity in this pathway (i.e. primary auditory cortices and anterior superior temporal sulci/gyri). Future research may investigate whether this "normalization" following tDCS can be linked to enhanced behavioral performance as well as documenting the time course of performance over several weeks.

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Figure 1. Illustration of brain activation in Patient ML. (A) Activation to any type of sound compared to silence pre-tDCS (blue) and post-tDCS (green). (B) Illustration of the contrast of activation in response to speech sounds post-tDCS minus pre-tDCS.